EDITORIAL

Novel aspects of oestrogen actions

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The biologicaly active oestrogen, 17β-oestradiol (E2) exerts, via the oestrogen receptor (ER), physiologcial responses outside of the reproductive tract. Important aspects of these novel actions of oestrogen in the brain, endocrine pancreas and large intestine, and actions mediated by extra-nuclear ER, are summarised in these *Journal of Physiology* Symposum reviews presented at the Annual Meeting of the Physiological Society in Dublin on 8 July 2009.

Oestrogen affects a wide range of physiological processes in reproduction, cardiovascular dynamics, cognition, electrolyte and fluid balance, cell excitability, proliferation, and differentiation. These effects are classically viewed as 'genomic', occurring over hours to days involving transcription and new protein synthesis and are initiated by E2 binding to the nuclear ER. Over the past four decades, evidence has accumulated for more rapid oestrogen responses (seconds to minutes) which involve membrane-associated oestrogen receptors (mER). These rapid responses to E2 have been termed 'non-genomic' and involve fast activation of signalling pathways such as protein kinases and calcium mobilization.

New evidence shows the latent genomic responses to oestrogen can be modulated by signalling events triggered during the rapid phase and vice versa, that there is transcriptional priming by E2 of the rapid phase responses. The reviews have highlighted the important role of rapid responses to oestrogen in physiological and disease states and the interplay between rapid and latent signalling and transcriptional events.

Although the first description of fast biological effects of oestrogen was demonstrated by Szego and Davis over forty years ago, advances in the field of rapid actions of E2 had been hampered, in the main, by lack of identity of the membrane receptors involved in transducing the rapid signalling effects and their physiological relevance

There is now firm evidence that the nuclear ERα and ERβ isoforms associate with the plasma membrane through palmitoylation and trafficking to caveolae rafts in the cell membrane through binding of ER to caveolin-1. The role of the membrane ER in diverse physiological responses and in disease states such as breast cancer are reviewed by Ellis Levin (2009). Characterization of the chaperone proteins and signalosome of the membrane oestrogen receptor is discussed in relation to current knowledge and future work required to characterise the biological regulation and function of a small pool of membrane-associated ER. The controversial topic of an oestrogenic role for the GPR30 receptor is also reviewed here and although the jury may still be out on this topic, the evidence from transgenic mouse models and *in vivo* studies favour functionally distinct and perhaps synergistic roles for GPR30 and ER.

Placing the rapid effects of oestrogen in a physiological perspective is an important topic in the review by Allan Herbison (2009) of the E2 novel actions in controlling fertility through suppressing the activity of gonadotropin releasing hormone (GnRH) neurons of the hypothalamus. The reviews by Angel Nadal (Nadal *et al.* 2009) and Fiona O'Mahony (O'Mahony *et al.* 2009) give good examples of 'priming' interactions between rapid and latent phases of E2 actions in the pancreatic β-cell and distal colon, respectively. Oestrogen has a stimulatory action on glucose-induced insulin secretion and on pancreatic β-cell survival which may have important protective effects in pregnancy to guard against gestational diabetes. The novel aspect of sexual dimorphism of oestrogen action on epithelial ion transporter activity and protein expression is reviewed by O'Mahony *et al.* (2009). The rapidly initiated and persistent anti-secretory response to E2 transduced via mERα in the distal colon is a good example of the interdependence and cross-talk between rapid and genomic responses necessary to achieve a full physiological response in the whole animal.

Valuable lessons in physiology are gained from these reviews. It is now evident that rapid responses to oestrogen are persistent over hours to days and can no longer be considered as being purely 'non-genomic' and effecting biological responses in isolation from the genomic actions of the hormone. While the reviews highlight novel actions of oestrogen in non-reproductive tissues, these are by no means to be considered as epiphenoma to the nuclear ER transduced responses controlling reproduction. Rapid physiological E2 responses occur in humans, e.g. at the level of circulatory and metabolic effects, rendering clinical significance to these rapid responses to oestrogen.

Key issues for future investigation include the molecular determinants underlying cross-talk between rapid and genomic oestrogen responses and, most importantly, understanding the physiological consequences of such interactions in whole tissues and animals over the physiological concentration of oestrogen. Transgenic mice with tissue-selective knock-out and knock-in of membrane and nuclear oestrogen receptors as well as selective agonists/antagonists of mER, ERα and ERβ will be essential tools in these investigations.

References

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